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Authors' Reply:

Drs. Belzberg and Rivkind have questioned our motivation and interpretation of the scientific and clinical literature regarding low-dose dopamine and its use in critically ill surgical patients. Our motivation for examining a routine practice in the case of low-dose "renal dopamine" was not based on cost containment or managed care or both but on an evidence-based examination of a routine practice. We agree that clinical and therapeutic decisions should be guided by theory, animal experiments, and well-designed human studies when available. The paper by Perdue et al.[1] attempted to examine the relevant literature for dopamine. We stand by our conclusions, in which we state that the routine use of *prophylactic* renal-dose dopamine in surgical patients is not supported by the literature. We agree that the diverse actions of dopamine suggest potential benefit from its use, but these benefits have never been proven to be clinically important in an adequately designed clinical trial in critically ill surgical patients The study by Hans et al.[2] referred to by Drs. Belzberg and Rivkind involved noncritically ill, nonhydrated patients undergoing arteriography and is not necessarily generalizable to ICU patients. The study by Flancbaum et al.[3] was a noncontrolled, nonrandomized study of surgical ICU patients that documented only dopamine-induced diuresis, not improved renal function.

The authors implore us to consider that most clinicians hold that low-dose dopamine improves renal perfusion and renal function. We agree that this may be a common belief and was a motivating factor behind our review. We certainly believe that a well-designed clinical trial of sufficient power to answer the question of whether low-dose renal dopamine is useful as either a "prophylactic or therapeutic" agent in preventing acute renal deterioration in critically ill patients would be a welcome addition to the literature. Low-dose dopamine may be indicated in patients who are well hydrated and need simultaneous augmentation of cardiac output and natriuresis. We believe, however, this should be in selected patients only and not on a routine basis. Questioning the practice of renal-dose dopamine in surgical patients has not been popular, but we believe its routine prophylactic use cannot be supported by the literature.

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To the Editor:

The paper by Wu et al.[1] analyzes the relationships between phenotypic expression in patients with familial adenomatous polyposis (FAP) and the site of mutations in the adenomatous polyposis coli (*APC*) gene and investigates the ability of APC mutations to predict surgical outcome.[1] Wu et al. found that mutations at codon 1309 and 1328 in exon 15G were associated with a uniformly severe polyposis phenotype~, and also that among the 43 patients (out of a series of 58 from 19 FAP kindreds) who initially underwent ileorectal anastomosis or partial colectomy, the rectum was later removed in eight. Seven of these patients had a mutation at codon 1309 or 1328. The use of mutational analysis to select the best surgical option has already been suggested by Vasen et al.,[2] who proposed performing ileorectal anastomosis for patients with APC mutation before codon 1250 and proctocolectomy with ileo pouch–anal anastomosis in those with APC mutation beyond codon 1250. We would like to make some comments on this issue and to discuss some new data, coming from a European collaborative study on a large series of FAP patients, in whom polyps and colorectal tumors, along with other less frequent tumors (e.g., thyroid carcinoma, hepatoblastoma, and desmoid tumors), have been investigated in detail.[3–8]

Genotype-phenotype correlations are not restricted to the number of colonic polyps, but also involve the variable risk of occurrence of extracolonic tumors. In fact, it has been suggested by Caspari et al.[3] and confirmed by our group[4] that desmoids are more frequent in patients with APC mutations beyond codon 1444, even if somatic mutations often occur at a codon different from that involved by the germline mutations.[4] On the contrary, thyroid carcinoma is restricted to female patients with mutations in exon 15 and 5′ to codon 1310 and is almost always associated with another extracolonic manifestation, *i.e.*, congenital hypertrophy of the retinal pigment epithelium.[5] In particular, we have found that (1) FAP-associated thyroid carcinoma shows a high incidence of ret-PTC activation in the tumoral tissue,[6] and (2) tumors showing this genetic alteration, despite multicentricity and early involvement of local lymph nodes, usually exhibit indolent behavior, which suggests that hyperradical procedures be avoided.[7,8] Hepatoblastoma also mainly occurs in patients with mutations in exon 15, but has also been observed in patients with mutations in the 5′ portion of the APC gene, such as mutations at codons 141, 215, 302, and 541, respectively.[9,10]

Severity of the FAP disease. In FAP patients, the severity of the disease cannot be defined simply on the basis of the number or early onset of colonic polyps. In fact, FAP is not merely a preneoplastic disease of the colon, but a genetically determined multitumoral syndrome. The diversity and the relative importance of the various tumors is wide, even in terms of life expectancy. In particular, there are some mutations, such as APC mutation at codon 1061, that currently are not considered high-risk mutations (in terms of number of polyps and colon cancer occurrence), but which in our study had a high incidence of both thyroid carcinoma and hepatoblastoma.[5–10] Both tumors always occur before the development of colon cancer and usually before the occurrence of colonic polyps. Both can cause death in the first decades of life.[6–10] In particular, hepatoblastoma can be lethal during childhood.

Surgical inferences from genetic analysis. There is legitimate hope that genetic analysis in the future will guide not only intensive screening but also surgical practice in patients with inherited multitumoral syndromes. Particularly in FAP patients, the planning of surgical treatment, in terms of extent of colon resection and selection of the reconstructive procedure, as well as the overall therapeutic strategy for patients with 5 or more extracolonic malignancies,[5,8] cannot be made without an accurate preoperative

genetic analysis. Whereas clinical inferences from mutational analysis seem to be justified, however, when specific oncogenetic alterations have already involved a given tissue (such as ret-PTC activation in patients with FAP-associated thyroid carcinoma),[6–8] caution is required while trying to speculate on the risk of occurrence of one type of tumor instead of another or to establish the severity of the multitumoral syndrome, simply on the basis of the germline mutation. In fact, a wide phenotypic variability has been observed not only within different kindreds carrying the same APC mutation, but also within the same kindred. Modifier genes and environmental factors, namely for some peculiar tumors such as thyroid carcinoma, play a major role in the occurrence of the malignant phenotype. In these cases, the germline APC mutation could only give a generic greater propensity to tumor development.[11] In conclusion, even if a better knowledge of carcinogenetic mechanisms is just around the corner and an intensive screening is legitimate for specific tumors showing an increased incidence in patients with a given germline mutation, caution is suggested before extrapolating surgical guidelines from mutational analysis and planning surgical treatment simply on the basis of germline mutations.

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Author's Reply:

Thank you for the opportunity to respond to the comments made by Cetta et al. about our work. They have pointed out that Vasen et al.[1] had already proposed using mutational analysis to select surgical options. The article by Vasen et al. was published in August 1996, and our paper was accepted by *Annals of Surgery* on July 3, 1996, so it is obvious that our discussion was written without knowledge of the Vasen paper. In fact, our results add a refinement to those of Vasen et al. in that we have identified two specific mutations in exon 15G associated with uniformly severe polyposis and a high risk of proctectomy. Vasen et al. merely suggest that all mutations 3′ of exon 1250 be viewed as high risk. We reported that mutations toward the 3′ end of exon 15 are associated with a mild phenotype and probably do not carry a high risk of proctectomy. In contrast to Vasen et al., we would not routinely perform proctectomy as an initial prophylactic surgery in patients so affected.

Cetta and colleagues go on to suggest that the severity of the disease cannot be defined simply on the basis age at onset or number of polyps. We agree that extraintestinal manifestations have a variable severity of expression that does not always correlate with the severity of the polyposis, and which seem to have their own peculiar genotype-phenotype correlations. However, the disease that kills patients with familial adenomatous polyposis is colorectal cancer, and risk of colorectal cancer is directly related to polyp number. The criterion of 1,000 polyps to distinguish mild from severe polyposis has been reinforced by Debinski et al.[2] and by our data. The absolute nature of the association between polyposis severity and 15G mutations is compelling and is born out in our retrospective surgical experience.

The word of caution left us by Cetta et al. at the conclusion of their remarks is appropriate. The choice of a surgical procedure in patients with familial adenomatous polyposis is sometimes difficult and complex. We do not suggest that knowledge of the germline mutation operating in the patient is the only factor in choosing an operation—rather that it may be of help in making the appropriate choice. Furthermore, knowledge of the germline mutation can help in other controversial areas, such as the age at which to begin endoscopic surveillance and the intensity of rectal surveillance after colectomy and ileorectal anastomosis.

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